**REMARKS/ARGUMENTS**

Claim 1 has been amended to recite that the apparatus is for "collecting whole blood," that the caspase inhibitor is present in an "amount effective to inhibit apoptosis," and that upon "collection, the whole blood is admixed with the stabilization agent and the anticoagulant." Support for the claimed subject matter as amended is contained throughout the specification, including for example, the disclosure in paragraphs [0011-0012], [0018] and [0032]. Claim 1 has also been amended to incorporate recitations contained in claims 3, 11, 20, and 24. Thus, these claims have been canceled and the dependencies of claims 4, 23, and 25-27 have been changed accordingly. Since the recitations of claim 11 (*i.e.*, that the stabilizing agent is "lyophilized"), claim 10 has also been canceled. Finally, claim 13 has been amended to recite that the stabilizing agent comprises "an admixture of" caspase inhibitors. Support for this claimed subject matter as amended is set forth throughout the specification, including, for example, the disclosure in paragraph [0042]. Thus, no new matter has been added. Applicants respectfully request entry of the amendments.

Claims 1, 3-11, 13-20, and 22-27 are under examination. Claims 28-76 stand withdrawn from consideration as being directed to a non-elected invention. The Office Action indicates that claims 1, 3-11, 13-20, and 22-27 have been rejected. By way of the present Request for Continued Examination, Applicants have made an earnest attempt to reduce the number of outstanding issues in order to expedite prosecution and obtain an indication of allowable subject matter.

Claims 1, 3-11, 13-20, and 22-27 have been rejected under 35 U.S.C. § 112, first paragraph, as non-enabled for an

apparatus that stabilizes any sample to any given degree in any given respect immediately upon its entering the apparatus. As stated in page 3, "the claims require that 'immediately on collection' that the cells or sample (*see* indefiniteness rejection below) be 'stabilize[d],' a requirement that is not supported by the specification or the contemporaneous art."

The rejection is now moot with respect to canceled claims 3, 10, 11, 20 and 24. The objectionable language, *i.e.*, "immediately on collection," has been deleted. As per the Examiner's suggestion, claim 1 now recites that upon "collection, the blood is admixed with the stabilization agent and the anti-coagulant." This newly added recitation thus requires physical contact between the stabilization agent and caspases that may be present in the collected blood which thus provides the manner of stabilization envisaged by the specification.

In view of the foregoing, reconsideration and withdrawal of the foregoing rejection under 35 USC § 112 are respectfully requested.

Claims 1, 3-11, 13-20, and 22-27 have been rejected under 35 USC § 112, second paragraph, as indefinite on the grounds that the recitations "biological sample" (taken in conjunction with the recitation "in an amount sufficient to stabilize cells"), "stabilization", "in an amount sufficient to stabilize cells," and "at least partially evacuated" are indefinite. The rejection is now moot with respect to cancelled claims 3, 10, 11, 20 and 24. Each of these objections will be addressed in turn with respect to the other claims.

The recitation "biological sample" has been deleted from claim 1 and replaced with the recitation "blood." Applicants submit that this amendment overcomes this ground of rejection.

The underlying basis for the allegation of

indefiniteness with respect to the term "stabilization," is set forth in pages 4-5 of the Office Action, is that the nature of the stabilization is not particularly pointed out in the claim or the specification. It is not clear whether the apparatus must simply physically stabilize the cells (*i.e.*, contain them) or whether some chemical or biological process is being promoted or discouraged by the components of the apparatus.

Claim 1 now recites that the stabilization agent, which comprises a lyophilized caspase inhibitor, is present in an amount effective to inhibit apoptosis, and thus clearly recites the nature of the stabilization achieved by the claimed invention. As stated above, inhibition of apoptosis is explicitly taught in the specification.

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

As set forth in page 5 of the Office Action, the Examiner's view is that even if the claims were amended to require that the sample comprises cells, which is now clear in view of the newly added recitation "whole blood," the specification provides insufficient guidance that the person of ordinary skill in the art could determine such an amount for each and every type of possible stabilization without undue experimentation. More specifically, the Examiner has alleged that the specification provides no guidance for identifying an amount of caspase inhibitor that is sufficient to, for example, stabilize white blood cells in the presence of high heat, stabilize skin cells in the presence of high levels of chaotropic agents, or stabilize sperm cells in the presence of ionizing radiation.

Initially, since this ground of objection has been raised under 35 USC § 112, second paragraph, Applicant submits that the claim recitation at issue would have had a clear and definite meaning to a person of ordinary skill in the art. To

the extent that a rejection under 35 USC § 112, first paragraph, was intended, Applicant submits that the claimed invention, as amended, is much more focused with respect to not only the types of cells that are to be stabilized (*i.e.*, cells contained in whole blood), but the type of stabilization intended, which in this case, includes inhibition against apoptosis. Contrary to allegations set forth in the Office Action, the specification does in fact provide guidance with respect to the quantity of the caspase inhibitor or admixture thereof that would be effective for the purpose of inhibiting apoptosis. Plainly, in view of this disclosure coupled with the knowledge extant in the field of the time the claimed invention was made, it would have allowed a person skilled in the art to identify an amount of caspase inhibitor that would be effective to inhibit apoptosis of cells contained in whole blood, without undue experimentation. The Examiner is invited to review paragraphs [0038] - [0043] of the specification in this regard. The Office Action does not provide any evidence or rationale as to why a person of ordinary skill would not have been able to identify such an effective amount in view of such disclosure.

In view of the foregoing, reconsideration and withdrawal of this ground of rejection under 35 USC § 112 are respectfully requested.

Finally, the recitation "at least partially evacuated" has been deleted in lieu of the current recitation "evacuated." While the text of the Office Action would certainly appear to indicate that the Examiner's primary concern lies with the phrase "at least partially," to the extent that there are any lingering concerns, Applicant respectfully submits that as evidenced by the disclosure in paragraph [0017], for example, the term "evacuated" would be readily understood by persons of ordinary skill in the field of blood collection apparati.

In view of the foregoing, reconsideration and withdrawal of this ground of rejection under 35 USC § 112 are respectfully requested.

Claims 1, 3-7, 10, 11, and 20 have been rejected under 35 USC § 102(b) as being anticipated by U.S. Patent 5,786,227, to Charlton ("*Charlton*"), taken in light of Wilhelm, *et al.*, Immunology Letters *59*:53-9 (1997) ("*Wilhelm*"). The Examiner alleges that *Charlton* teaches an apparatus for biological sample collection that comprises two tubes, one inside the other, wherein the inner tube has a membrane that is partially coated with sodium azide, which is contained within the tube in dry form, and that the tube has a cap to seal the first end, and that when the sample is collected in the outer tube and the inner tube is subsequently inserted, the sample transfers from the outer tube through the filter into the inner tube, such that the outer tube is "evacuated" in that the sample moves from the outer tube into the inner tube, and that as evidenced by the *Wilhelm* Publication, sodium azide is a caspase inhibitor.

The rejection is now moot with respect to cancelled claims 3, 10, 11 and 20. Applicant respectfully disagrees that Charlton anticipates the other claims.

The fluid collection, filtration and storage devices described in *Charlton* are distinguishable from the claimed apparatus in at least two respects: namely, i) that it does not contain a caspase inhibitor; and ii) it is not evacuated. Accordingly, Applicant respectfully submits that *Charlton* is not an anticipatory publication.

In column 5, lines 11-12, *Charlton* teaches that any number of materials may be present on the filter so that they will mix with the sample, and that for biological samples, the material will generally include a preservative, *e.g.*, sodium azide. *Charlton* does not teach or in any way suggest that the

preservatives generally, or even sodium azide in particular, includes or is actually a caspase inhibitor. The *Wilhelm* Publication, which has been cited as evidence that sodium azide is, in fact, a caspase inhibitor, actually teaches the opposite, i.e., that sodium azide induces caspase activity. As explained in her accompanying Declaration under 37 C.F.R. § 1.132, the inventor, Dr. Rainen, states that based on her own review and analysis of this publication, it reports, both explicitly and by way of illustration, that sodium azide induces caspase activity and apoptosis. In addition, she explains that the only "inhibitory" activity described in *Wilhelm* relates to its affect on VP-16. This is expressly stated in paragraph 3.7 of *Wilhelm* that is quoted in the Rainen Declaration and is reproduced below:

> 3.7 *Azide inhibits caspase-activation by VP-16*
>
> A family of cyseine proteases termed caspases [9] is thought to be essential for apoptosis and to become activated following an apoptotic signal [10]. A closely related subgroup of these caspases is able to cleae the cellular enzyme poly (ADP-ribose) polymerase after the peptide sequence DEVD [11] and such activity appears to be critical for apoptosis folling most if not all stimuli including etoposide [12,13]. We measured this activity as the ability to cleave the fluorogenic substrate DEVD-AMC (Fig. 6). ***Azide alone induced some DEVD-AMC-cleaving activity over a period of 8 h demonstrating further its ability to induce apoptosis.*** VP-16 caused strong activation of these proteases whereas azide completely inhibited the caspase-activating effect of VP-16 when both agents were present. (emphasis added)

Thus, the preservative taught by *Charlton* is just that, a preservative, and not a caspase inhibitor as required by Claim 1.

As set forth in page 7 of the Office Action, the Examiner has taken the position that *Charlton's* outer tube is evacuated in the sense that the sample moves from the outer tube to the inner tube. As evidenced by the disclosure in paragraph [0017], the term "evacuated" as recited in the present claims refers to an internal pressure that is sufficiently low to draw a predetermined volume of a biological sample, *e.g.*, whole blood, into the tube. The Examiner has not pointed to any specific disclosure in *Charlton* that teaches that the outer tube or inner tube is "evacuated" as that term would be understood in the context of the presently claimed invention.

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1, 3-7, 10, 11, 13-20, and 22-27 have been rejected under § 103(a) as unpatentable over *Charlton* taken in view of U.S. Patent 6,184,210, to Keana, *et al.* ("*Keana*"), and *Wilhelm*. The Examiner has acknowledged that *Charlton* does not teach an embodiment in which the apparatus comprises two or more caspase inhibitors, or an embodiment in which the stabilizing agent is lyophilized or comprises heparin with the components in claims 15-19. However, the Examiner contends that *Keana* teaches compositions comprising caspase inhibitors can further comprise antioxidants, anticoagulants, buffering agents or reducing agents, and that one of ordinary skill in the art would recognize that simply having dried sodium azide is close enough to having lyophilized azide since the chemical properties would predictably be similar and thus obvious. The Examiner has also determined that it would have been obvious to add a known anticoagulant such as EDTA, citrate, or heparin to the tube of the apparatus since this is a known technique to improve the storage of blood. The Examiner concludes that a person of ordinary skill would have had a reasonable expectation of success in combining the component of *Keana* with the caspase

inhibitor in the apparatus of *Charlton*, because *Keana* teaches that these components are compatible with caspase inhibitors.

The rejection is now moot with respect to cancelled claims 3, 10, 11, 20 and 24. Applicant respectfully traverses this rejection as it applies to the other claims.

The collective teachings of *Charlton* and *Wilhelm* do not establish a prior art teaching of a caspase inhibitor disposed in a tube, let alone a tube having the structural elements as recited in the presently amended claims. The teachings in *Keana* do not remedy this deficiency. *Keana's* patented invention is directed to caspase (or cell death) inhibitors that can be used primarily in clinical settings to retard or block cell death in a variety of conditions in which the loss of cells, tissues or entire organs occurs. In the Summary, *Keana* teaches that these inhibitors, referred to as dipeptides, may be useful in reducing, preventing or preventing maladies in which apoptotic cell death is either a causative factor or a result. In column 9, lines 18-26, *Keana* adds that the lifespans of mammalian cell lines and yeast cells that are commonly used to produce large amounts of recombinant proteins for industrial or medicinal use can be extended by including the cell death inhibitors in the growth medium.

The allegations set forth on page 9 of the Office Action (*i.e.*, that *Keana* teaches that the compositions comprising caspase inhibitors can further comprise antioxidants, anticoagulants, buffering agents, or reducing agents) ignores the fact that *Keana* contemplates the use of cell death inhibitors to extend the life of cell lines in a growth medium, in transplanted tissue, etc. and not in the context of blood collection. Even those working examples in *Keana* which involve *in vitro* experiments entail contacting the dipeptide apoptosis inhibitors disclosed therein with various cells in multi-well dishes. *See* column 17, lines 4-13 of *Keana* in this regard.

Plainly, these are not blood collection tubes as required by the presently claimed invention.

Claims 8 and 9 have been rejected under § 103(a) as being unpatentable over *Charlton*, *Keana*, and *Wilhelm* as applied to claims 1, 3-7, 10, 11, 13-20, and 22-27, and further in view of U.S. Patent 5,788,862, to Degen, *et al.* ("*Degen*"). The Examiner has acknowledged that the references cited in the prior rejection do not teach an embodiment in which the stabilizing member is a gel that is physically separate from the stabilizing agent. *Degen* is alleged to teach an apparatus in which the membrane filter is a gel and can also be used to filter blood. The determination reached by the Examiner is that since both filters taught by *Degen* and *Charlton* can be used to filter blood, it would have been obvious to a person skilled in the art that this is the simple substitution of known membranes used for the same purpose and will predictably achieve the same result. Regarding the separation of the stabilizing member in the stabilizing agent, the Examiner has determined that since *Charlton* allegedly teaches that the azide is near to mix with the biological sample, one of ordinary skill would recognize that the azide would have the same effect if added to the tube itself and not integrated to the filter, since the chemical properties of the azide would remain unchanged, and that the act of making components of an apparatus integral or separable are matters of obvious engineering choice by the inventors. Applicant respectfully traverses this rejection.

Regardless of what *Degen* may or may not teach with respect to separating members, it remains that the collective teachings of *Charlton*, *Keana*, and *Wilhelm* do not establish *prima facie* obviousness with respect to claims 1, 4-7, 13-19, 22, 23, and 25-27. *Degen* simply deals with filtration mediums and not preservation of cells in a collected blood sample.

In view of the foregoing, reconsideration and withdrawal of the above rejection are respectfully requested.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone Applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: September 2, 2009

Respectfully submitted,
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